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The role of interleukin-6 in the early diagnosis of sepsis in premature infants

Mehrdad Mirzarahimi, Manouchehr Barak, Abdolkarim Eslami, Afsaneh Enteshari-Moghaddam

Department of Pediatrics, School of Medicine, Ardabil University of Medical Science, Ardabil, Iran

Abstract

Septicemia is one of the major causes of mortality and morbidity in newborns. The aim of this study was to investigate the role of interleukin-6 (IL-6) in the early diagnosis of Sepsis in premature newborns. This cross-sectional study was conducted on preterm infants admitted to NICU of Hospital Buali in Ardabil city, Iran. C-reactive protein (CRP), IL-6 and complete blood count tests have been done in baseline, third and seventh day. Collected data analyzed by one-sample t-test, repeated measures and ANOVA in SPSS.21. The mean of IL-6 in the first and third day after hospitalization was significantly more than normal value. The mean of CRP in the third and seventh day after hospitalization significantly more than normal value. We found that increasing in IL-6 level can occur earlier than CRP and it can be used as a good index in early sepsis diagnosis compare than CRP.

Introduction

Bacterial sepsis with the incidence of 1-5 in 1000 live births is one of the major causes of neonatal morbidity and mortality and may be occur due to exposure to infection during childbirth and its clinical manifestations may appear at birth time or during the first days of life.[1] During the first three days of life, early neonatal Septicemia is associated with high risk of death (mortality higher than 15-50%) and long-term severe neurological problems. Prevalence and mortality of neonatal septicemia is increased by decreasing gestational age and the risk of death from it in premature infants was more.[2] Neonatal septicemia risk increase with various factors such as premature birth, low birth weight, premature and prolonged rupture of membranes, maternal colonization with group B streptococcus, histologic chorioamnionitis and mother infections during or after childbirth.[3] Quick identification of infected infants (especially premature infants) and on time antibiotic treatment is crucial but unreliability of clinical symptoms and lack of good diagnostic tests, precise and early detection of septicemia is difficult.[1,2] Sick infants are usually treated by various antibiotics while a few of them have not infection.[1] Many proprietary and non-specific methods were used for diagnosis of septicemia in infants in before but they have less sensitivity. In numerous clinical and laboratory studies in recent years, different inflammatory cytokines including IL-6, IL-8, tumor necrosis factor have been suggested as early and valuable indicators in the diagnosis of neonatal septicemia.[1,2,4,5]

A meta-analysis study showed that IL-6 can be a valid marker for predicting neonatal sepsis and early diagnosis of sepsis in neonatal care units.[6]

According to the pathogenesis of early neonatal sepsis, changes in cytokines and acute phase reactants can be one of the earliest signs in the diagnosis of septicemia and since an increase in CRP in infants is considered as a factor for neonatal sepsis, we decided by checking the serum levels of IL-6 and CRP during the first week of life and studying their values approved the predictive role of IL-6 in the early diagnosis of sepsis in premature infants.

Materials and Methods

Type of study and patients

This cross-sectional study conducted on 31 premature infants admitted to the neonatal intensive care unit (NICU) during the first week afer given birth.

Experiments

For all premature infants, blood culture was done in admision and CBC, IL-6, CRP experiments were cheked until 7 days after birth. Written informed consent was taken from parents of all infants and the design of study approved by Ethics committee of Ardabil University of Medical Science. To Measure IL-6 and C-reactive protein we used standardized methods used before by other studies.[7,8]

Statistical analysis

Collected data analyzed by statistical methods and all statistical analysis were performed using SPSS.21. The $P<0.05$ was considered statistical significant.

Results

Among of all infants, 15 (48%) were girl and 16 (52%) were boy; 21 (67.7%) was born by cesarean delivery. The mean length of hospitalization in the boys and girls were 11.3 and 10.4 days, respectively. The mean of IL-6 in the first and third days after hospitalization was significantly higher than normal. The mean of CRP in the third and seventh days after hospitalization was significantly higher than normal. The average of absolute value of neutrophils in the first, third and seventh days after hospitalization was significantly higher than normal. The changes at IL-6 levels during study times was signifiant ($P=0.007$), so that these rates in the seventh day compared to first and third days were 86.2% and 80.4%, respectively (Figure 1A).

The changes at CRP levels during study times was signifiant ($P=0.005$), so that these rates in the seventh day compared to third day was 29.1% and in the third day compared to first day was 92.7% (Figure 1B).

The changes at Neutrophil amonts during study times was signifiant ($P=0.009$), so that these rates in the seventh day compared to first and third days were 69.2% and 19.7%, respectively (Figure 1C).

Discussion

The results of this study showed that the

Correspondence: Afsaneh Enteshari-Moghaddam, Department of Internal Medicine, Faculty of Medicine, Ardabil University of Medical Science, Ardabil, Iran.
E-mail: af.enteshari@arums.ac.ir

Key words: Neonatal Sepsis, Premature newborns, Interleukin-6, CRP.

Aknowledgments: The results of this study financially suported by Ardabil University of Medical Science and authors would like to tanks all infants and their parents which participated in the study.

Contributions: the authors contributed equally.

Conflict of interest: the authors declare no potential conflict of interest.

Received for publication: 10 July 2017.
Revision received: 22 July 2017.
Accepted for publication: 23 July 2017.

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Licensee PAGEPress, Italy
Pediatric Reports 2017; 9:7305
doi:10.4081/pr.2017.7305

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average of IL-6 on the first and third day of hospitalization was significantly higher than normal. Also the mean of IL-6 on the seventh day of hospitalization was lower than normal, but this difference was not statistically significant. There was a significant difference between the average of IL-6 in different time periods (P=0.007).

Some studies showed that the IL-6 has higher sensitivity and spesifity than the other biomarkers in ealrly diagnosis of sepsis which was similar to our study results.[9,10]

Adib *et al*. showed that the mean of IL-6 in infants with positive blood cultures was 117.49 pg/ml and its level significantly was more than two groups of infants with negative blood cultures (having 2 to 3 symptoms of sepsis) and healthy infants (without sepsis symptoms).[11]

Heidarzadeh *et al*. in a study showed that IL-6 plasma level has a predictive value in the diagnosis of neonatal sepsis.[7]

Buck *et al.* in a prospective study investigated the use of IL-6 and CRP measurment in the diagnosis of sepsis in 222 infants and showed that increasing concentration of IL-6 in 73% of infants, infected with positive blood culture, and in 87% of infants with clinical diagnosis of sepsis, but negative culture, were observed.[8]

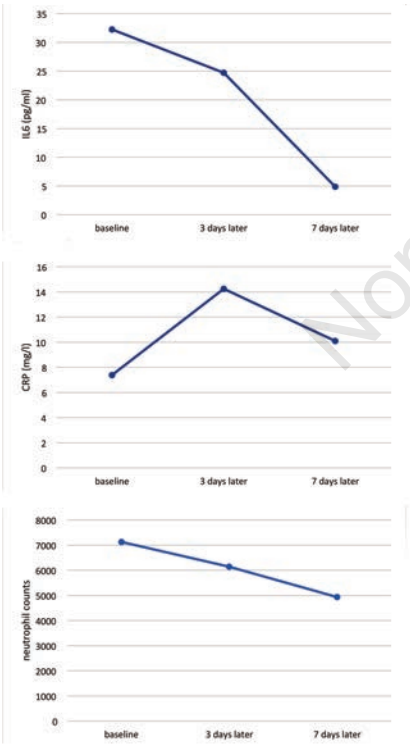

Figure 1. A) Changes level of interleukin-6 (pg/mL) and B) C-reactive protein (mg/L) during study days; C) neutrophil counts during study days.

Many studies showed that levels of IL-6 in the first 48 hours of life in premature infants is significantly high which in line with our study. [12-16]

Our study showed that the mean CRP on the first, third and seventh days of hospitalization were significantly different from the normal value. There was a significant difference between the mean of CRP in different time periods (P=0.005).

Some studies showed that IL-6 as an early diagnosis marker for bacterial sepsis in patients with liver cirrhosis which was in line with our study results.[17-19]

The difference between the mean of the infants' CRP on the first and third days (P=0.006) and the third and seventh days (P=0.007) was significant. It means that CRP level increased during the first three days and then began to decline in the third and seventh days. Adib *et al.* obtained the average amount and level of CRP with 18-22 mg/mL in the group of infants with positive blood cultures was sign ificantly higher than other infants. Døllner *et al*.[1] in a study showed that CRP is a diagnostic test for infection in infants and more accuracy was observed in the combination of CRP and IL-6.[1] The results of a study conducted by Kocabaş *et al.* showed that the mean of CRP level, in infants suffering from sepsis, at baseline was significantly more than healthy infants.[12] Also in the third and seventh days of treatment, compared with baseline, CRP levels decreased in 17 improving infants while these values were dramatically increased in 9 infants who died during treatment. The results of this study are in line the findings of Adib *et al.* and Døllner *et al.* studies,[1] but it is inconsistent with the findings of Kocabaş *et al*. study.[12] In this study, CRP levels increased in the third day and reveales that the amount of CRP increases a bit late and reduced with treatment continues.

The results of this study revealed that the mean absolute neutrophil level on the first, third and seventh days of hospitalization was significantly higher than neutropenia index. There was statistically significant. Also there was a significant difference between the mean absolute neutrophil levels in time periods. There was no significant difference between the mean absolute neutrophil level of infants in the first and third days of hospitalization. But the difference between the mean absolute neutrophil level of infants on the first and seventh days (P=0.004) and the third and seventh days (P=0.027) was significant.

Conclusions

Results showed that IL-6 can be a valid marker for predicting neonatal sepsis and be considered as a good tool for early diagnosis of sepsis in neonatal care units compared to CRP.

Limitation of study

Because of more negative cases seen in blood culture test result we could not use blood culture as a marker for early diagnosis sepsis, so due to this limitation and also the main aim of this study, we only used clinical marker such as IL-6 to identify the sepsis diagnosis and the results of blood culture not included in this paper.

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